REMARKS

Claim Amendment

Claims 5 and 18 have been amended, Claim 19 has been canceled and new Claim 66 has been added.

Claim 5 has been amended to recite "wherein said isolated TCL-1 protein is a full-length TCL-1 protein." Support for this amendment can be found, for example, at page 7, lines 1-8, FIG. 3A and page 9, line 35 to page 10, line 9.

Claim 18 has been amended to recite "[a]n isolated TCL-1 protein derivative comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence depicted as SEQ ID NO:2, over a contiguous sequence of at least 100 amino acids, whereby said isolated TCL-1 protein derivative binds to an antibody that also binds to the TCL-1 protein of SEQ ID NO:2." Support for this amendment can be found, for example, at page 10, lines 6-25.

Support for new Claim 66 can be found, for example, at page 9, lines 33-34.

The claim amendments and new Claim 66 are supported by the specification as filed. Therefore, this Amendment adds no new matter. As described below, Applicants believe that this Amendment places all pending claims (i.e., Claims 5-7, 13, 17, 18 and 66) in condition for allowance. Entry of the Amendment is respectfully requested.

Rejection of Claims 18 and 19 Under 35 U.S.C. § 112, First Paragraph

Claims 18 and 19 stand rejected under 35 U.S.C. § 112, first paragraph. With respect to Applicants' previous claim amendments and remarks, the Examiner states that although Applicants have amended Claims 18 and 19 to recite a higher degree of identity (i.e., having at least 90% amino acid sequence identity), the claims are still drawn to a broad genus, such that one of skill in the art would not reasonably conclude that Applicants had possession of the claimed genus (Office Action, page 2, lines 12-17). The Examiner asserts that Applicants have

not disclosed a structure-function relationship between sequences having 90% amino acid identity and at least a contiguous sequence of at least 25 or 50 amino acids as recited in Claims 18 and 19, respectively, and that the question remains as to what domains confer the requisite function (Office Action, page 2, lines 17-21).

While disagreeing with the Examiner's assertions and to expedite allowance of the pending claims, Applicants have canceled Claim 19 and amended Claim 18 to recite "[a]n isolated TCL-1 protein derivative comprising an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence depicted as SEQ ID NO:2, over a contiguous sequence of at least 100 amino acids, whereby said isolated TCL-1 protein derivative binds to an antibody that also binds to the TCL-1 protein of SEQ ID NO:2." As amended, the claimed protein derivatives possess the structural requirement of having at least 90% amino acid sequence identity to SEQ ID NO:2 over a contiguous sequence of at least 100 amino acids, and the functional requirement of binding to an antibody that also binds to the TCL-1 protein of SEQ ID NO:2. Given that the amino acid sequence of TCL-1 is only 114 amino acids in length (see, e.g., FIG. 3A of the specification), and that the claimed protein derivatives must possess at least 90% amino acid sequence identity to SEQ ID NO:2 over a contiguous sequence of at least 100 amino acids (i.e., the majority of the 114-amino acid TCL-1 protein), it is clear that the claimed protein derivatives would contain numerous epitopes that would fulfill the functional requirement of binding to an antibody that also binds to the TCL-1 protein of SEQ ID NO:2. For example, Kuby *et al.* teach:

> *Complex proteins contain multiple overlapping B-cell epitopes.* Until recently, it was dogma in immunology that a given globular protein had a small number of epitopes, each confined to a highly accessible region and determined by the overall conformation of the protein. However, it has been shown recently that most of the surface of a globular protein is potentially antigenic. This has been demonstrated by comparing the antigen-binding profiles of different monoclonal antibodies to various globular proteins. For example, when 64 different monoclonal antibodies to BSA were compared for their ability to bind to a panel of 10 different mammalian albumins, 25 different overlapping antigen-binding profiles emerge, suggesting that these 64 different antibodies recognized a minimum of 25 different epitopes on BSA. Similar findings have emerged for other globular proteins, such as

> myoglobin and HEL. The surface of a protein, then, must present a large number of potential antigenic sites.

Kuby, J., *Immunology*, 2nd. ed. (W.H. Freeman & Co., New York, 1991), p. 96, left-hand column, emphasis added (cited as Reference C3 in the Supplemental Information Disclosure Statement being filed concurrently herewith).

With regard to the size of a protein epitope or antigenic determinant, the teachings of Kuby describe early studies by Elvin A. Kabat that used carbohydrate antigens to suggest that an antibody's binding site was a cleft of sufficient size to bind six or seven amino acid or sugar residues (Kuby, J., *Immunology*, 2nd. ed. (W.H. Freeman & Co., New York, 1991), p. 92, paragraph spanning left and right-hand columns). Further, as cited by the Examiner in a previous Office Action, Hancock *et al.* teach that "the optimum-sized peptide for generating antisera is from 10-20 amino acid residues in length, although peptides as small as 8 residues in length may be used to generate antisera" (see Hancock, D.C., *et al.*, "Synthesis of Peptides for Use as Immunogens" in *Methods in Molecular Biology, Vol. 80: Immunochemical Protocols, 2nd ed.* (J.D. Pound, ed., Humana Press, Totowa, NJ, 1998), p. 71, section 1.1.3) (cited in Office Action dated March 30, 2005, page 10, lines 8-12). More recent studies have revealed that for globular protein antigens, their epitopes are dependent on the tertiary conformation of the native protein and can involve a greater number of amino acid residues on the surface of the antigen and the antibody (see, e.g., Kuby, J., *Immunology*, 2nd. ed. (W.H. Freeman & Co., New York, 1991), p. 93, paragraph spanning left and right-hand columns). Nevertheless, it is clear that in view of the large number of epitopes or antigenic determinants that are present on a globular protein, such as the TCL-1 protein derivative claimed in Claim 18, and the high degree of sequence identity between the claimed TCL-1 protein derivatives and the TCL-1 protein of SEQ ID NO:2 (i.e., at least 90% amino acid sequence identity to SEQ ID NO:2 over a contiguous sequence of at least 100 amino acids), the claimed protein derivatives would fulfill the functional requirement of binding to an antibody that also binds to the TCL-1 protein of SEQ ID NO:2. Therefore, the skilled artisan would have concluded that Applicants were in possession of the protein derivatives of Claim 18, as amended, at the time the instant application was filed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 18 and 19 under 35 U.S.C. § 112, first paragraph.

Advisory Action Before the Filing of an Appeal Brief

In the Advisory Action Before the Filing of an Appeal Brief ("Advisory Action") dated April 13, 2006, the Examiner refused to enter Applicants' Amendment After Final Rejection, stating that the proposed amendments raise new issues that require further consideration and/or search (Advisory Action, Section 3). The Examiner further asserts that the amended claims failed to satisfy the written description requirement because Claim 5 was not limited to full length sequences (Advisory Action, Continuation Sheet (Continuation of Section 3)). While disagreeing with the Examiner, Claim 5 has been amended to recite that "said isolated TCL-1 protein is a full-length TCL-1 protein", in order to expedite allowance of the claimed subject matter

Additionally, the Examiner asserts in the Advisory Action that as to Claim 18, the specification fails to disclose what 90% of the sequence is required and that it is recognized in the art that epitopes are based on conformation and configuration, and not contiguousness as argued by Applicants (Advisory Action, Continuation Sheet, Continuation of Section 3). As described above and in the previously-filed Amendment After Final Rejection, Applicants have amended Claim 18 to recite that the isolated TCL-1 protein derivative comprises an amino acid sequence having at least 90% amino acid sequence identity to the amino acid sequence depicted as SEQ ID NO:2, over a contiguous sequence of at least 100 amino acids. Given the large number of epitopes or antigenic determinants that are present on a globular protein (e.g., as taught by Kuby *et al.*) and the high degree of sequence identity between the claimed TCL-1 protein derivatives and the TCL-1 protein of SEQ ID NO:2 (i.e., at least 90% amino acid sequence identity to SEQ ID NO:2 over a contiguous sequence of at least 100 amino acids), the claimed protein derivatives (which possess the structural requirement of being encoded by a nucleic acid that hybridizes under specified stringent conditions to a nucleic acid consisting of the complement of SEQ ID NO:1 from nucleotide 49 to 387) would fulfill the functional requirement of binding to an antibody that also binds to the TCL-1 protein of SEQ ID NO:2. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of Claim 18 under 35 U.S.C. § 112, first paragraph.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the IDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Paul Alloway

Paul G. Alloway
Registration No. 58,286
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

Dated: 4/20/2006